

Response to Office Action
Application No. 09/457,926
Attorney's Docket No. 032367-449 (AMI-061-R2)
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2 Please amend Claim 51 as follows:

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51. (Amended) The compound according to Claim 41, wherein L" is a vancomycin moiety which is attached to the linker at the carboxy terminus of the vancomycin moiety.

REMARKS

Applicants respectfully request that this application be reconsidered in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 41-46, 49-51, 53-55, 57 and 58 are currently pending in this application. Of these pending claims, Claims 42, 44-46, 57 and 58 have been withdrawn from consideration by the Examiner as being drawn to non-elected species. Accordingly, Claims 41, 43, 49-51 and 53-55 are currently pending for examination on the merits.

In the event that a generic claim is found allowable, Applicants respectfully request consideration of any of the withdrawn claims which are written in dependent form or which otherwise include all the limitations of the allowed generic claim as provided by 37 C.F.R. §1.141.

2. Summary of the Amendments

Claims 50 and 51 have been amended to more clearly define and distinctly claim the subject matter Applicants regard as their invention. Specifically, Claims 50 and 51 have been simplified by deleting the vancomycin structure and, in place thereof, reciting the point of attachment of the vancomycin moiety to the linker. Support for these amendments is found, for example, on page 38, lines 10-20. Additionally, Claims 50 and 51 have been amended to depend from Claim 41 instead of Claim 48 in view of the prior cancellation of Claim 48.

Pursuant to 37 C.F.R. §1.121, a marked-up version of the amended claims showing the changes made is attached. Entry of these amendments is respectfully requested.

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3. Rejections Under 37 C.F.R. §103

Claims 41, 43, 49-51 and 53-55 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,693,791, issued to Truett; in view of Boeckh et al., *Antimicrob. Agents Chemother.*, 1988, 32(1), 92-95; Renound-Grappin et al., *Antiviral Chem. and Chemotherapy*, 1998, 9(3), 205-223; and Staroske et al., *Tet. Lett.* 1998, 39, 4917-4920. For the following reasons, this rejection is respectfully traversed.

A. Requirements for Establishing a *Prima Facie* Case of Obviousness

To establish a *prima facie* case of obviousness, three requirements must be satisfied. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify the references or to combine the references in a manner that produces the claimed invention. See, *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

Second, the proposed modification of the prior art must have had a reasonable expectation of success as determined from the vantage point of the skilled artisan at the time the invention was made. See, *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See, *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Additionally, the above teachings or suggestions, as well as the expectation of success, must come from the prior art, not from applicant's own disclosure. See, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

B. Applicants' Presently Claimed Invention

Applicants' presently claimed invention is directed to specifically defined chemical compounds having a β -lactam moiety covalently linked through a linker to a vancomycin moiety. The β -lactam and vancomycin moieties are attached to the linker through

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specifically defined points of attachment. Applicants invention is also directed to pharmaceutical compositions containing such compounds.

C. The Examiner's Rejection

The Examiner has concluded that Applicants' presently claimed invention is *prima facie* obvious in view of the cited references for the following reasons:

"[I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of Truett concerning the linking of diverse antibiotic moieties combined with the teaching of Boeckh et al to perform combination therapy using the drugs, the teaching of Renoud-Grappin concerning linking drugs to perform combination therapy and the teaching of Staroske et al concerning vancomycin dimers linked through the amino and carboxy terminus. Specifically, Truett teaches that two antibiotics, one known to attack Gram positive bacteria and another to attack Gram negative bacteria can be linked and the advantages of doing such, and Boeckh et al teach that vancomycin and ceftazidime fulfill these requirements. Renoud-Grappin teach that one way to achieve effective combination therapy is to covalently link two different drugs. Finally, Staroske et al teach that vancomycin can be linked at specific linkage sites. One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains. One of ordinary skill would also have had a reasonable expectation of success based on the fact that Staroske et al teaches linking chemistry for vancomycin."

For the following reasons, Applicants respectfully disagree with this conclusion.

D. Motivation

The first inquiry when determining whether a *prima facie* case of obviousness is appropriate is whether the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, provides the requisite suggestion or incentive to motivate the skilled artisan to modify the references in a manner that produces the claimed invention.

In the present case, the Examiner has not suggested, nor is it reasonable to suggest, that the Truett reference alone provides the necessary motivation to make Applicants'

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presently claimed invention. The Truett reference discloses that various antibiotic moieties can be linked together using diisocyanates, dianhydrides, diacid chlorides, diepoxides and carbodiimides (see Column 1, lines 5-15). However, the particular types of antibiotics that Truett indicates can be linked together are described as follows:

"The types of antibiotics that can be linked are sulfonamides, trimethoprim, penicillins and related structures, cephalosporins and related structures, chloramphenicol, erythromycin, metronidazole, quinolones, tetracyclines and aminoglycosides." (Column 6, lines 34-38)

Thus, the Truett reference does not teach or suggest the use of a glycopeptide antibiotic, such as vancomycin, for the preparation of antibiotic dimers. Since the Truett reference lacks the disclosure of any glycopeptide antibiotic, this reference cannot provide the necessary motivation on its own to link vancomycin to a β -lactam antibiotic, such as ceftazidime.

Recognizing this limitation, the Examiner has first combined the Truett reference with the Boeckh reference which teaches combination therapy using vancomycin and ceftazidime. However, the Boeckh reference merely discloses physical mixtures of vancomycin and ceftazidime. Accordingly, this reference also does not provide any suggestion or motivation on its own to chemically link vancomycin to ceftazidime.

In combining these references, however, the Examiner has argued that "Truett teaches that two antibiotics, one known to attack Gram positive bacteria and another to attack Gram negative bacteria can be linked and the advantages of doing such, and Boeckh et al teach that vancomycin and ceftazidime fulfill these requirements."

In response, Applicants first take issue with the Examiner's statement that Truett teaches the advantages of linking two antibiotics together. Specifically, Applicants respectfully point out that the Truett reference does not explicitly state any particular advantage to be gained by linking antibiotic compounds together. At best, Truett states in Column 1, lines 24-30 that "[i]t has been realized that the linking of two antibiotic moieties functioning in different fashions...*can be of value*" and "[t]wo antibiotic moieties can also be linked in which one is known to attack Gram positive bacteria and another to

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attack Gram negative bacteria, and this new entity is *of value*" (emphasis added). Beyond stating that the linked antibiotics have "value" (i.e., presumably that such dimers have utility), no particular advantage is described by Truett for such compounds. In fact, the Truett reference only provides data for a dimer of p-aminobenzene sulfonamide and sulfapyridine and, with regard to these compounds, Truett indicates that "[a]ll products showed *modest* inhibition zones in the vicinity of the filter paper tabs containing the product fractions" (emphasis added) (Column 45, lines 62-64). Thus, the Truett reference fails to state any explicit advantage to be gained by linking antibiotic moieties together and demonstrates that when such dimers are prepared the products showed only "modest" inhibition zones.

Accordingly, in view of the fact that physical mixtures of vancomycin and ceftazidime are reported to be effective for treating infections (as evidenced by the teachings of the Boeckh reference) and Truett neither reports nor demonstrates any explicit advantage for the linked antibiotics disclosed therein, the combined disclosures of these references would not provide sufficient motivation to the skilled artisan to modify the teachings of these references in a manner to produce Applicants' presently claimed invention.

The Examiner has addressed this issue by also citing the Renoud-Grappin reference and arguing that "Renoud-Grappin teach that one way to achieve effective combination therapy is to covalently link two different drugs." However, the Examiner's statement is inaccurate – the Renoud-Grappin reference actually only speculates that one way to achieve effective combination therapy is through the use of heterodimers, but their actual results show that the heterodimer approach did not work in their case. In this regard, the Examiner's attention is directed to page 219, second column and, in particular, to the first full paragraph where the authors state "[s]everal reasons may explain the *failure* of this heteodimer approach to increase the inhibitory activity against HIV" (emphasis added).

Accordingly, rather than providing the requisite suggestion or incentive to motivate one skilled in the art to prepare heterodimers, the Renoud-Grappin reference actually teaches away from the preparation of heterodimers by demonstrating that the disclosed heterodimers did not provide any advantage. Again, this information, when combined

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with the knowledge that physical mixtures of vancomycin and ceftazidime were known to be effective for treating infections, would actually lead one skilled in the art to use physical mixtures of antibiotics and not to prepare heterodimers because no actual advantage is demonstrated for heterodimers.

The Examiner has also cited the Staroske reference for its teaching of "head-to-head" and "head-to-tail" dimers of vancomycin and, additionally, for its teaching that there is a "strong incentive for the development of more potent antibiotics". In particular, the Examiner has pointed out the teaching in this reference on page 4918 that dimeric vancomycin compounds exhibit improved antibacterial activity.

In response, Applicants respectfully note that, although this reference does indicate that certain vancomycin dimers had increased antibacterial activity against a particular strain of resistant bacteria, the reference clearly goes on to say in the same sentence that such dimers "were still insufficiently active for therapeutic use" (page 4918, first paragraph). Thus, the only data provided by this reference actually shows that the vancomycin dimers discussed therein were insufficiently active for therapeutic use against the resistant strain of bacteria.

Thus, in summary, the Truett reference teaches that linking of two antibiotic moieties together "can be of value" but reports that "[a]ll products showed *modest* inhibition zones". The Renoud-Grappin reference adds to this by teaching that the heterodimer approach failed to increase the inhibitory activity of the disclosed compounds against HIV. The Staroske reference further teaches that the vancomycin dimers discussed therein were insufficiently active for therapeutic use against a particular strain of resistant bacteria. The Bocckh reference, however, teaches that physical mixtures of vancomycin and ceftazidime are therapeutically effective. Accordingly, when taken as a whole, the cited references clearly provide no incentive for the skilled artisan to depart from the use of physical mixtures of vancomycin and ceftazidime and prepare heterodimers of such compounds. This is especially true when one considers that more effort is typically required to prepare heterodimers compared to monomers and therefore, one skilled in the art would only be motivated to prepare such heterodimers if an actual advantage is to be gained over the monomers.

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Moreover, in view of the actual results reported in the cited references, the generalized statements in these documents regarding possible benefits of heterodimers can, at best, be viewed as making heterodimers "obvious to try" or as providing an "invitation to explore" the field of heterodimers. The courts, however, have long held that "obvious to try" or an "invitation to explore" does not create a *prima facie* case of obviousness. See, *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988); and *Ex parte Obukowicz*, 27 U.S.P.Q.2d 1063 (B.P.A.I. 1992).

Finally, Applicants also note there is no structural similarity between any of the chemical structures disclosed in the cited references and Applicants' present claimed compounds, i.e., the presently claimed compounds are not homologs, analogs or isomers of the prior art compounds of record. Thus, structural similarity does not provide the requisite motivation or suggestion to modify the known compounds in a manner which produces Applicants' presently claimed compounds.

Accordingly, for the foregoing reasons, Applicants respectfully submit that the cited references do not provide the requisite motivation necessary to establish a *prima facie* case of obviousness for the presently claimed subject matter.

E. Reasonable Expectation of Success

The second requirement for establishing a *prima facie* case of obviousness is that the proposed modification of the prior art must have had a reasonable expectation of success as determined from the vantage point of the skilled artisan at the time the invention was made.

In the present case, the Examiner has stated that "[o]ne of ordinary skill would also have had a reasonable expectation of success based on the fact that Staroske et al teaches linking chemistry for vancomycin." Presumably, the Examiner is saying that one skilled in the art would have had a reasonable expectation that heterodimers of vancomycin and ceftazidime could be prepared successfully based in the linking chemistry taught by the Staroske reference for vancomycin.

However, this argument fails to address the issue of whether one skilled in the art would have had a reasonable expectation that such heterodimers would be effective as

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antibiotics. In this regard, it was well-known in the art at the time the present invention was made that structural modifications of biologically active compounds, such as β -lactams and glycopeptides, significantly affect the biological activity or efficacy of such compounds and the scientific literature is replete with publications describing the structure/activity relationships for β -lactam derivatives and glycopeptide derivatives.

In the present case, the linking together of vancomycin and ceftazime significantly changes the chemical structure of both vancomycin and ceftazime. In view of these significant structural changes, one skilled in the art could not have predicted *a priori* whether a covalently-linked vancomycin – ceftazime dimer would have antibacterial activity because such chemical modifications are outside the scope of the traditional structure/activity relationships understood by those skilled in the art for these compounds (as demonstrated by the fact that there are no structurally similar compounds reported in the art).

Applicants acknowledge that the Staroske reference teaches that glycopeptide dimers retain antibacterial activity – but such dimers are known to mimic the naturally-occurring *in situ* association of glycopeptide antibiotics reported to be important for their activity. See, for example, page 4917, second paragraph of the Staroske reference which states that “[r]ecent studies report that back-to-back dimerisation of these antibiotics (except teicoplanin) is important to their antibacterial activity”.

In contrast, there is nothing in the prior art of record that suggests that vancomycin modified with a ceftazime moiety would retain its antibacterial activity or alternatively, that ceftazime modified with a vancomycin moiety would retain its antibacterial activity. Thus, one skilled in the art would not have had a reasonable expectation that modifying the cited references to provide a vancomycin – ceftazime heterodimer would succeed in producing a compound having antibacterial properties.

Additionally, in view of the failure of the heterodimer approach as reported in the Renoud-Grappin reference, one skilled in the art would certainly have no reasonable expectation that covalently linking vancomycin and ceftazidime would successfully “create a broad spectrum antibiotic compound to fight antibiotic resistant strains” which the Examiner has stated would be the motivation of the skilled artisan in view of the cited

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references.

Accordingly, Applicants respectfully submit that the cited references do not provide the necessary reasonable expectation of success required to establish a *prima facie* case of obviousness.

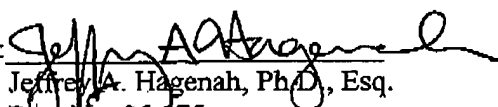
In summary, for the foregoing reasons, Applicants respectfully submit that the cited references provide no motivation or suggestion to make the specific chemical compounds of the instant claims. Additionally, one skilled in the art would not have had a reasonable expectation that combining the references in the manner suggested by the Examiner would succeed in producing compounds having antibiotic properties. Thus, the cited references fail to establish a *prima facie* case of obviousness for the presently claimed subject matter. Accordingly, Applicants respectfully request that the rejection of Claims 41, 43, 49-51 and 53-55 under 35 U.S.C. §103(a) be withdrawn.

For the foregoing reasons, Applicants believe that this application is now in condition for allowance. Should there be any remaining issues that can be resolved by telephone, the Examiner is respectfully requested to telephone the undersigned attorney at (650) 808-6406.

Respectfully submitted,

ADVANCED MEDICINE, INC.

Dated: March 18, 2002

By: 
Jeffrey A. Hagenah, Ph.D., Esq.
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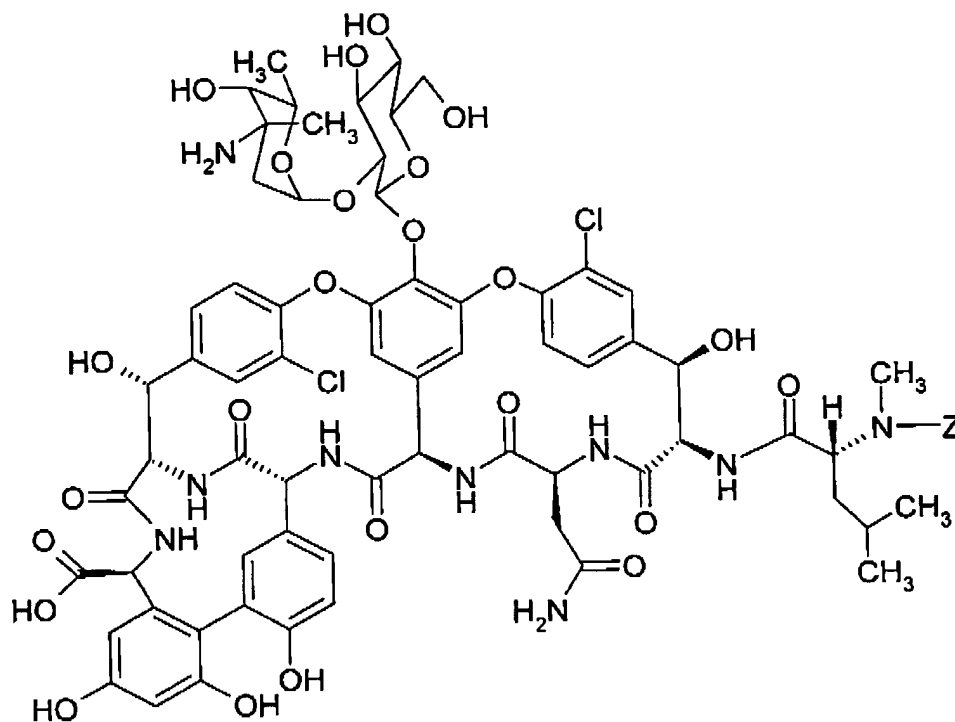
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VERSION OF AMENDMENTS WITH MARKINGS TO SHOW CHANGES MADE

Please amend Claim 50 as follows:

50. (Amended) The compound according to Claim [48] 41, wherein L" is a vancomycin moiety which is attached to the linker at the amino terminus of the vancomycin moiety [represented by the formula:

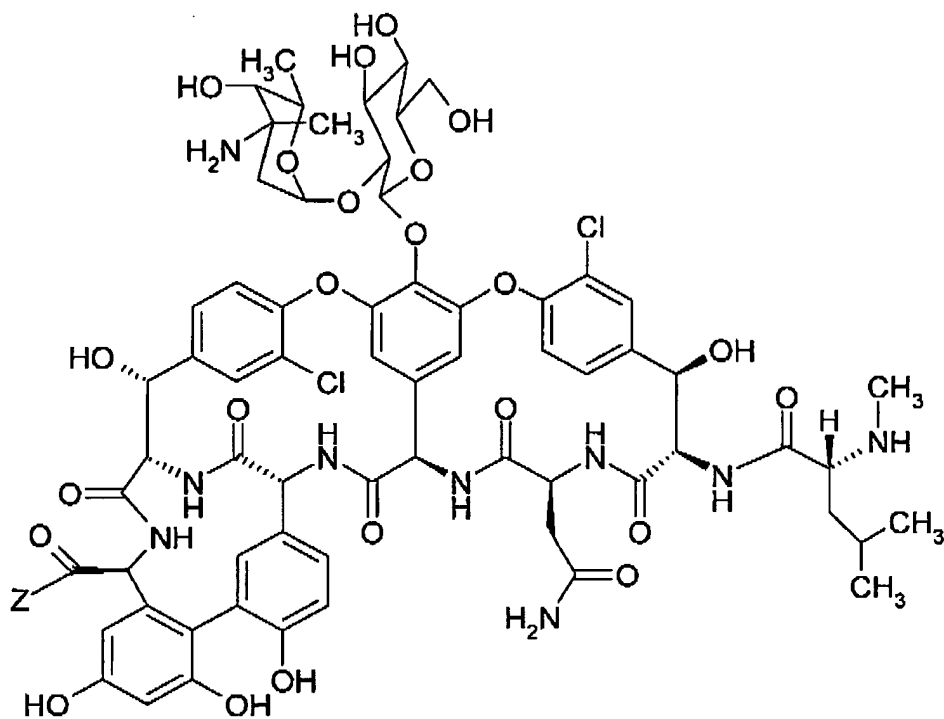


wherein Z is the point of linkage for the vancomycin moiety to the linker moiety X].

Please amend Claim 51 as follows:

51. (Amended) The compound according to Claim [48] 41, wherein L" is a vancomycin moiety which is attached to the linker at the carboxy terminus of the vancomycin moiety [represented by the formula:

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wherein Z is the point of linkage for the vancomycin moiety to the linker moiety X].